SUMMARY OF THE HEALTH EFFECTS OF CHROMIUM

HEALTH STUDIES SERVICE
SPECIAL STUDIES AND SERVICES BRANCH
ONTARIO MINISTRY OF LABOUR

Prepared by: J. M. O'Heany, M.D.

January 1986

Revised: September 1986

TABLE OF CONTENTS

1. Introduction 1

2. Chemical and Physical Properties 1

3. Toxicology 2
   - 3.1 Absorption 3
     - 3.1.1 Gastrointestinal Absorption 3
     - 3.1.2 Respiratory Absorption 5
     - 3.1.3 Percutaneous Absorption 5
   - 3.2 Transport and Metabolism 6
     - 3.2.1 Diffusion and Binding 6
     - 3.2.2 Placental Permeability 7
   - 3.3 Excretion 7

4. Health Effects 7
   - 4.1 Acute Health Effects 7
   - 4.2 Chronic Health Effects 8
     - 4.2.1 Hypersensitivity 8
     - 4.2.2 Irritant Effects 9
       - 4.2.2.(a) Skin Ulceration 9
     - 4.2.3 Other Irritant and Miscellaneous Findings 9
     - 4.2.4 Reproductive Effects 10
     - 4.2.5 Carcinogenicity 11
       - 4.2.5.(a) Epidemiological Evidence 11
       - 4.2.5.(b) Genotoxicity 13
       - 4.2.5.(c) Animal Studies 14

5. Summary of Toxicology and Health Effects 14

6. Conclusions 15
   - 6.1 General 15
   - 6.2 Carcinogenesis 16
   - 6.3 Dose-Response Relationships 16
   - 6.4 Occupational Exposure Limits 17

7. Recommendations 19

CHROMIUM

1. Introduction

This document is a summary of the health effects of chromium and its compounds. Occupational exposure to chromium occurs in a number of industries. Exposure to chromium metal and/or alloys exists for welders, ferrochrome and other alloy workers. Mixed exposure to hexavalent and trivalent chromium compounds occurs in leather tanning, chromate and ferrochrome productions, welding, chromium electroplating and cement production and use. Exposure to hexavalent chromium compounds occurs in the production of chromium pigments and in the production of some products containing chromium pigments.

This document examines the chemical and physical properties of chromium as well as the toxicological and epidemiological evidence of its health effects. Conclusions are drawn as to the relationship of the level of exposure to the production of health effects, and suggestions for maximum levels of airborne exposure to various classes of chromium compounds are made.

More detailed information can be found in the document "Effects of Chromium Compounds on Human Health", prepared by McMaster University, Hamilton, Ontario for the Ontario Ministry of Labour (Nieboer et al., 1984).

2. Chemical and Physical Properties

Metallic chromium is steel gray in colour, melts at 1857°C $\pm$ 20°C, boils at 2672°C, and has a specific gravity of 7.20 at 28°C (Weast, 1980).
Chromium exists in a number of valence states from -2 to +6, all of which are not of equal stability. The most common valence states are +3 and +6.
Chromium is found in nature most commonly in the form of chromite. Elemental chromium does not occur naturally. The average concentration of chromium in the earth's crust is about 200 ppm and in sea water about 2 ppb. The concentration of chromium in drinking water supplies is usually below 10 ppb. The daily intake of chromium by man has been estimated to be about 60 µg (30 - 100 µg), of which about 10 µg is contributed by water (Hammond, 1980; Kumpulainen, 1979).

Chemically, the Cr(III) state is the most stable form of chromium. Cr(VI) rarely occurs in nature because it is easily reduced by oxidizable organic matter. Cr(VI) occurs most commonly in the form of chromate or dichromate, both of which are produced in industry. The presence of Cr(VI) in the environment is important because this valence state of chromium is believed to be the most toxic.

3. Toxicology

The toxicity of chromium compounds is believed to be related to their valence state and to the solubility of the compounds. The carcinogenic potential of chromates has been traditionally associated with their water solubility. Metal chromates may be divided into three arbitrary categories, as is illustrated in Table 1. The first group may be designated as sparingly soluble to insoluble and includes chromates of zinc, lead, barium and strontium. Of intermediate solubility are calcium chromate and potassium dichromate. The third solubility category includes the highly soluble potassium and sodium chromates, as well as sodium dichromate.

Biological media such as serum and cytosol have a high affinity for metal ions (e.g., Zn^{2+}, Pb^{2+}, Ba^{2+}) and contain reducing agents that can react with chromate, and for these reasons, the solubility of metal chromates may be expected to be augmented in biological solutions.

Particle size influences the deposition and retention of particles in the bronchial tree. This factor may be of equal or greater importance than water solubility in the absorption of inhaled chromium (Langard, 1983).

Chromium is an essential trace element which when accumulated in excess can become toxic. In patients who have been receiving long-term intravenous therapy, weight loss and peripheral neuropathy have been observed. This clinical picture has been attributed to chromium deficiency, and following the administration of chromium, the patient's general condition has been noted to improve. The daily chromium requirement of man has not been established with certainty, however,

according to the EPA (1984, p.2-7), the average American intake of 50 to 200 µg/day is considered adequate, because, at this level no symptoms of chromium deficiency have been noted.

3.1 Absorption

Chromium can be absorbed through the gastrointestinal and respiratory tracts and to a lesser degree through the skin.

3.1.1 Gastrointestinal Absorption

Under non-industrial exposure conditions the gastrointestinal tract is the most important route of uptake. Gastrointestinal absorption is significantly influenced by the valence state of the chromium. Inorganic trivalent chromium compounds are less readily absorbed in man and animals than are hexavalent compounds. Donaldson and Barreras (1966) have demonstrated that human gastric fluids reduce Cr (VI) to Cr (III) and in this way absorption is diminished. Although precise quantification of absorption is not possible a reasonable estimate of gastrointestinal absorption in adults of both trivalent and hexavalent chromium is between 0.5 and 3% (Donaldson and Barreras, 1966; Underwood, 1977).

Table 1

Water Solubility of Metal Chromates [a,b]

	Compound	Molecular Weight (amu)	g/L	moles/L	Temp. (°C)
1.	$ZnCrO_4$	181.4	insol.	insol.	25
	$Zn_x(CrO_4)_y(OH)_z$ (basic Zn chromates)	—	slightly sol.[c]	slightly sol.	25
	$PbCrO_4.PbO$	564.4	insol.	insol.	25
	$PbCrO_4$	323.2	5.8×10^{-4}	1.8×10^{-6}	25
	$Pb_2(OH)_2CrO_4$	564.4	0.14	2.5×10^{-4}	17
	$BaCrO_4$	253.3	4.4×10^{-3}	1.7×10^{-5}	28
	$SrCrO_4$	203.6	1.2	5.9×10^{-3}	15
2.	$K_2Cr_2O_7$	294.2	49 (1020)	0.17 (3.5)	0 (100)
	$CaCrO_4\ 2H_2O$	192.1	163	0.85	20
3.	K_2CrO_4	194.2	629	3.2	20
	Na_2CrO_4	162.0	873	5.4	30
	$Na_2Cr_2O_7$	262.0	2380	9.1	0

a From Weast (1973) and IARC (1980).

b When values are calculated from the solubility products quoted in Sillen and Martell (1964), there are small discrepancies.

c Likely to be in the order of 1 g/L.

1. sparingly soluble
2. intermediate solubility
3. highly soluble

3.1.2 Respiratory Absorption

In occupational exposures to chromium the respiratory tract is the most significant route of entry. Absorption of inhaled chromium compounds is related to valence, solubility, particle size distribution and the lung clearance rates of the individual compounds. The literature concerning respiratory absorption of chromium in man is limited to a few published reports of chromium exposed workers. The chromium exposure in different work situations varies depending upon the specific chromium compound or compounds as well as the other variables listed above. Generalized statements describing respiratory absorption rates of the various forms of chromium compounds are at present not possible.

Studies of small cohorts of welders working on high alloy Cr-Ni steel (Tola et al. 1977; Glyseth et al. 1977) have attempted to relate exposure to chromium in air to the level of urinary excretion of chromium. Water-soluble chromium (most of which was reported to be hexavalent) showed the best correlation between air and urine levels, followed by total chromium. The concentration of water insoluble chromium in the air failed to show a significant correlation with urine levels of chromium.

3.1.3 Percutaneous Absorption

Percutaneous absorption of chromium through unbroken skin is dependent on valence state, concentration, nature of the specific salt and the pH of the applied solution. Some hexavalent chromium compounds are believed to diffuse freely through the epidermis while trivalent chromium compounds move less freely (Mali et al., 1963). Hexavalent chromium compounds readily penetrate cell membranes and are believed to be reduced to trivalent chromium by intracellular

components. Trivalent compounds do not penetrate the skin as readily as hexavalent compounds. Damage to the epidermis permits the uptake of trivalent chromium and probably increases the rate of absorption of hexavalent chromium.

3.2 Transport and Metabolism

3.2.1 Diffusion and Binding

The mechanism of uptake of hexavalent chromium (Cr(VI)) has been more completely explained than the uptake of trivalent chromium (Cr(III)). It is believed that Cr(VI) enters the epithelial cell by means of simple diffusion across the cell membrane and to some extent as a result of phagocytosis. Once inside the cell, reduction of Cr(VI) to Cr(III) takes place using electrons available from donor groups such as glutathione (GSH), NADPH and NADH. However, the oxidizing power of chromate at physiologic pH is reduced and therefore both Cr(III) and Cr(VI) are present in the cytoplasm. Cr(VI) which has not been reduced to Cr(III) can leave the cell by diffusion and enter the bloodstream. In the blood Cr(VI) enters the red blood cells (RBC). Inside the RBC Cr(VI) is reduced to Cr(III) most of which is then bound to hemoglobin. Trivalent chromium in the plasma is transported bound to serum proteins, mainly transferrin. Chromium transported by the blood is distributed to other organs with the greatest retention by the spleen, liver and bone marrow. The mechanism of uptake and the transfer of Cr(III) across the cell membrane has not been completely explained; under some circumstances Cr(III) may cross the cell membranes, but not as readily as does Cr(VI).

3.2.2 Placental Permeability

The limited data available indicates that small amounts of both chromium (III) and (VI) are transferred from mother to offspring. Further discussion can be found in 5.2.3.

3.3 Excretion

The kidneys and the gastrointestinal tract are the major routes for the excretion of chromium (Mertz, 1969). More recent research supports the concept that biliary excretion plays an important role in the gastrointestinal excretion of chromium (Cikrt and Bencko, 1979; Sayato et al. 1980).

Absorbed chromium is eliminated from the body in a rapid phase (1-2 days), representing clearance from the blood and in a slower phase representing clearance from tissues. Adipose and muscle tissue retain chromium for about two weeks, while the liver and spleen may store chromium for as long as 12 months. Estimated half-lives for whole body chromium in rats, determined using radioisotope labelled chromium, are 22 and 92 days for Cr(VI) and Cr(III) respectively (Sayato et al., 1980).

4. Health Effects

4.1 Acute Health Effects

There are no studies in which chromium metal has been reported to produce any acute toxic effects in man.

Hexavalent chromium compounds are the cause of most of the health problems associated with exposure to chromium. They are irritating and corrosive and readily absorbed from the lung, gut and under some circumstances, the skin.

Acute systemic poisoning with hexavalent chromium is rare. It may follow deliberate or accidental ingestion or be the result of absorption through cut or abraded skin. Oral administration of high doses of Cr(VI) compounds will result in gastric corrosion. The oral LD_{50} of sodium dichromate in humans has been estimated to be 50 mg/kg (NIOSH, 1979). The kidney appears to be the main target in acute chromium toxicity. Acute renal and hepatic failure have been reported following exposure to Cr(VI) compounds at levels of 1-2 mg Cr(VI) per kg of body weight or greater. However, there is very little scientific literature available on this subject.

4.2 Chronic Health Effects

4.2.1 Hypersensitivity

Chromium compounds may cause damage to the skin. Pure metallic chromium, however, does not harm the skin by contact (Pederson, 1982). Skin reactions to chromium compounds are of two types: primary irritant reactions (i.e., chrome ulcers) and allergic contact dermatitis.

Chromium is the second most common skin allergen in the general population, nickel being the most common (Polak, 1973). In men, however, chromium is the most frequent sensitizer (Cronin, 1980). Chromium dermatitis is particularly common in the construction industry and is attributed to the presence of chromates in cement. Cases of chromium allergy have also been seen in other occupations where there is exposure to chromates. Hexavalent chromium compounds are generally accepted to be more potent inducers and elicitors of sensitivity than trivalent compounds. After initial sensitization, which is usually due to hexavalent chromium compounds,

subsequent allergic responses may be elicited by either hexavalent or trivalent chromium compounds. It would appear that the concentration of trivalent chromium necessary to produce an allergic reaction in persons allergic to chromium is higher than the corresponding dose of hexavalent chromium (Fregert, 1964).

Chromates have also been associated with occupational asthma. The evidence is limited and is based on a number of case reports and case series studies.

4.2.2 Irritant Effects

4.2.2.(a) Skin Ulceration

Ulceration of the skin (usually referred to as chrome ulcers) is the most common lesion resulting from occupational exposure to hexavalent chromium compounds (Bidstrup, 1971, 1983). The lesions begin as single or multiple papular lesions on the exposed skin usually in areas which are exposed to trauma. The surface ulcerates and eventually leaves a punched out area with an undermined border. The ulcers are as a rule painless, penetrate deeply, and may reach the underlying bone. Neoplastic change in the ulcer does not usually occur. Patients with chrome ulcers rarely are allergic to chromates.

4.2.3 Other Irritant and Miscellaneous Findings

Occupational exposure to hexavalent chromium compounds may result in perforation of the nasal septum and has also been reported to cause irritation of the respiratory tract, "pneumoconiosis", bronchitis, chronic lung congestion and possible liver and kidney damage. Chest x-rays carried out on workers exposed to dust containing chromium have been

reported to have exaggerated pulmonary markings (Government of India, 1953), and nodular fibrosis and ventilatory impairment (Princi, 1962).

4.2.4 Reproductive Effects

There is no evidence that chromium compounds have produced birth defects or reproductive deficits in man.

Limited work has been reported on the reproductive effects of chromium in animals. In feeding studies both hexavalent chromium (Cr(VI)) and trivalent chromium (Cr(III)) compounds have been found to cross the placental barrier in animals and enter the fetus during mid to late gestation. Fetal uptake of Cr(VI) was greater than that of Cr(III). In most of the studies it was shown that in pregnant rodents exposed to inorganic chromium only a very small fraction of the administered dose was transported to the fetus in utero. Estimations of the percentage of the dose transferred to the fetus varied from zero to 12% Cr(VI) and 0.4% of Cr(III) (Danielsson et al. 1982). In contrast to these studies when chromium, in the form of "glucose tolerance factor" synthesized by brewer's yeast, was administered to rats by stomach tube during gestation, from 20 to 50% of this chromium was detected in the litters (Mertz, 1969). This is consistent with the role of chromium as an essential trace element. Developmental defects attributed to Cr(VI) and Cr(III) varied from species to species but included cleft palate and skeletal defects. In hamsters a single intravenous dose of 8 mg/kg of chromium trioxide on day 8 of gestation resulted in an increased incidence of cleft palates in the young when examined on day 15 of gestation (Gale, 1982). The malformations were strain specific (3 strains responding and three strains showing no response). While several of the studies reported fetal malformations only when maternal toxicity was

present, not all studies reported the state of maternal health. Definitive conclusions concerning the correlation between fetal abnormalities and maternal toxicity cannot be made at this time. The data available indicate that the observed teratogenic effects may well be the secondary result of maternal toxicity.

Based on experimental studies using rodents (rats, mice and hamsters) it can be shown that chromium can cross the placenta. Placental transport appears to be time dependent and is greatest when the chromium is administered shortly before birth.

No animal studies concerning reproductive effects were found where the exposure to Cr(VI) or Cr(III) was by inhalation.

4.2.5 Carcinogenicity

4.2.5.(a) Epidemiological Evidence

The risk of lung cancer has been consistently shown to be high in the chromate producing industry, where exposure is to a mixture of insoluble (largely trivalent) and both moderately soluble and soluble (largely hexavalent) chromium compounds. The strength of the association of exposure in the chromate production industry with lung cancer is evident from the high lung cancer mortality ratios found in various studies, the consistency of results reported by different investigators in different countries, the dose-response-relationship found in several studies, and the specificity of the tumour site (i.e., the lung). The standardized mortality ratio (SMR) for respiratory cancer in chromate producing workers was found to be as high as 29 by Brinton et al. (1952) and as low as 2.0 by Korallus et al. (1982). The variation in mortality ratios across studies may be the result of differences in exposure intensity and duration, length

of observation period, or percentages of the cohorts lost to follow-up. The magnitude of the mortality ratios found in several studies gives strong support to the association of exposure in the chromate producing industry with an increased incidence of lung cancer.

In the chromate-pigment production industry, where the exposure is mainly to sparingly soluble hexavalent chromium compounds, a high risk for lung cancer was also demonstrated in several studies conducted in different countries (Langard and Norseth, 1975, 1979; Langard, 1983; Cooper, 1983; Davies, 1978, 1979, 1984).

In the ferrochromium producing industry, where workers are exposed to a mixture of forms of chromium (which is predominantly metallic and trivalent, but nevertheless contains 10-30% soluble hexavalent chromium), the possibility of an increased risk of lung cancer has also been raised. However, the relative risks reported were considerably lower than those generally experienced in chromate production. Since there have been conflicting reports, and in view of the various methodological problems in the studies, the findings of an increased risk of respiratory cancer in this industry should be regarded as tentative (Langard et al. 1980; Axelsson et al., 1980).

An increased risk of lung cancer has also been reported for chromium platers exposed primarily to highly soluble chromates. Again, the limited number of studies, the low strength of association and the lack of consistency of the association leave some room to question these findings, but the suggestion of a dose-response relationship in several of these studies (e.g., Waterhouse, 1980; Franchini et al. 1983) is certainly suggestive of a causal relationship.

4.2.5.(b) Genotoxicity

The results of in vitro and in vivo assays of genotoxicity have supported the potential for Cr(VI) to be the carcinogenic species. All hexavalent chromium compounds have consistently demonstrated positive mutagenic activity in a number of bacterial test systems. This activity was demonstrated in the absence of a metabolic activation system. In the presence of a metabolic activation system, the mutagenic activity of Cr(VI) disappeared. Because Cr(VI) shows only marginal, if any, mutagenic activity after metabolic activation, it has been suggested that the mammalian enzymes or cofactors in the activation system reduced Cr(VI) to Cr(III). Both Cr(III) and Cr(VI) have been demonstrated to interact with DNA in bacterial assays. Cr(VI) has inhibited DNA synthesis but increased unscheduled DNA synthesis in mammalian cells in culture. Research carried out by Stella et al. (1982) demonstrated cytotoxic activity in cultures of stimulated human lymphocytes using both Cr(VI) and Cr(III). These in vitro studies demonstrated clearly that the activity was valence dependent as, compared with the dose of Cr(VI), almost 100 times the dose of Cr(III) was required to produce a similar effect. A slowing down of the mitotic cycle due to the cytotoxic action of Cr(VI) and Cr(III) has been described by other authors (Levis et al. 1979; White et al. 1979), in different mammalian cell lines and they observed an even greater increased cytotoxicity in Cr(VI) compounds as compared with Cr(III) compounds than was shown by Stella et al. (1982).

4.2.5.(c) Animal Studies

Hexavalent chromium compounds have not been reported to induce a significantly increased incidence of tumours in

laboratory animals following exposure by inhalation or ingestion. Similar negative results have been obtained following the ingestion of trivalent chromium compounds; however these studies have not been reported in detail. There is some evidence that chromium, particularly some hexavalent chromium compounds, is carcinogenic following subcutaneous injection or intrabronchial, intrapleural, intramuscular, or intratracheal implantation. However, tumours have only consistently been demonstrated using intramuscular implantation. Tumours at the site of injection or implantation have been associated with a large number of chemicals and substances, all of which do not have human carcinogenic potential. Of all the chromium salts, calcium chromate is the only one that has been consistently found to be carcinogenic in rats by several routes of administration. Although the studies available indicate that metallic chromium powder and trivalent chromium compounds are not carcinogenic, these compounds have been studied less extensively than hexavalent chromium compounds. The relevance of studies using intramuscular implantation in animals to evaluating the risk to persons exposed to inhalation or ingestion of chromium compounds is questionable.

5. Summary of Toxicology and Health Effects

An increased incidence of respiratory cancer has been established for chromate production, chromium chemical production and chromate pigment production workers. The risk for chrome platers would appear less certain and that for ferrochromium workers, spray painters and welders may be considered equivocal. Cancers at other sites, specifically cancers of the gastrointestinal tract, nasal and laryngeal cancers, have been noted to be slightly increased in some studies but this finding has not been consistently reported.

Bioassays and related in vitro experiments indicate that all hexavalent chromates (both soluble and insoluble) can induce mutations and cause chromosomal damage. Positive animal carcinogenicity data are only convincing for calcium chromate (intermediate solubility), lead chromate (sparingly soluble), and perhaps for a number of compounds (strontium and chromic chromates), which are sparingly soluble. For trivalent chromium, the animal studies show no consistent carcinogenic potential. Only when very large concentrations are employed, or when a special ligand environment is generated around Cr(III), can mutagenicity be demonstrated as a result of exposure to trivalent chromium compounds.

6. Conclusions

6.1 General

Chromium compounds are the second most common skin allergen in the general population. Both hexavalent and trivalent chromium compounds are allergenic. Hexavalent chromium compounds are more efficient in inducing and eliciting contact sensitivity reactions than trivalent compounds. Respiratory sensitivity to chromium compounds is known but is rare.

Chromium compounds may also produce a primary irritant reaction. Ulceration of the skin and nasal septum are frequently reported. Hexavalent chromium compounds are believed to be the cause.

6.2 Carcinogenesis

Since the 1930s, studies have shown that there is an increased risk of carcinogenesis associated with exposure to some

chromates. There is positive epidemiological evidence which has related respiratory cancer in workers to previous exposure to chromate production, chromium chemical production and chromate pigment production. The data available for chrome platers is somewhat less certain, and that for ferrochromium workers, welders and spray painters would appear to be equivocal.

Although the available epidemiological evidence does not permit a clear distinction between the relative carcinogenicity of different hexavalent chromium compounds, exposure to sparingly soluble hexavalent chromium compounds has been clearly shown to be associated with an increased risk of respiratory carcinogenesis in humans. Exposure to trivalent chromium compounds, when not associated with exposure to hexavalent compounds, has not been proven to be associated with an increased risk of respiratory carcinogenesis.

6.3 Dose-Response Relationships

In reviewing the epidemiologic evidence the available exposure data was considered. Unfortunately, as Langard (1983) has pointed out, even when atmospheric concentrations of the substance(s) in question are cited in these studies, usually measurements have only been carried out for a short time at the end of the observation period (e.g., Machle and Gregorius, 1948; Mancuso and Hueper, 1951; Mancuso, 1951; Gafafer, 1953; Langard and Norseth, 1975; Langard et al., 1980; and Axelsson et al., 1980). Such measurements do not correspond to the period of exposure which is the focus of the epidemiological study, and they do not provide data about the average level of exposure or changes in exposure over time.

The dose-response data available for carcinogenesis are inadequate to allow a quantitative risk assessment, which precludes an evaluation of risk at low levels of exposure. It is apparent that the information is not suitable to equate exposure with risk on a quantitative basis (Hayes, 1980, 1982; Langard, 1983).

6.4 Occupational Exposure Limits

From an occupational health viewpoint the valence states of significance for chromium are +3 and +6. A wide range of chromium metal alloys and inorganic compounds exist in industry. These compounds vary significantly in their toxic and carcinogenic properties. For this reason, it is necessary to consider chromium and its inorganic compounds as a number of separate, but related groups:

1. Chromium metal and alloys.
2. Divalent chromium compounds (Cr^{2+}).
3. Trivalent compounds (Cr^{3+}).
4. Hexavalent chromium compounds (Cr^{6+}).

Chromium metal and alloys, divalent chromium compounds, and trivalent chromium compounds (1., 2. and 3. above) are considered to have a low order of toxicity. Dermatitis has been reported in workers handling trivalent chromium compounds (Fregert, 1965). A time-weighted average exposure of 0.5 mg/m^3 (measured as total chromium) as recommended by the ACGIH should protect workers from toxic effects such as, dermatitis and pulmonary disease.

Hexavalent chromium compounds (4. above) have been demonstrated to be carcinogenic on the basis of epidemiologic investigations of workers and experimental studies in animals.

There does not appear to be any evidence which would support the establishment of a safe level of exposure to these compounds, nor does there appear to be data upon which a risk estimate could be formulated to estimate a "safe" level. It is recommended that a time-weighted average concentration of chromium (VI) in air, as low as reasonably achievable, be adopted.

7. Recommendations

In the Province of Ontario it is recommended that Chromium and its Inorganic Compounds be regulated according to the following plan:

1. Chromium Metal and Alloys
2. Divalent Chromium Compounds
3. Trivalent Chromium Compounds

These three groups should be treated as a single group and exposure should be at or below a Time-Weighted Average (TWA) exposure of 0.5 mg per cubic metre (measured as total chromium).

4. Hexavalent Chromium Compounds.

It is recommended that exposure to these compounds be controlled at a time-weighted average (TWA) concentration of chromium (VI) in air as low as reasonably achievable and in any case the level should not exceed 0.02 mg per cubic metre of air (measured as chromium (VI)), with a ceiling value of 0.05 mg per cubic metre of air (measured as chromium (VI)), for any fifteen minute period.

In cases where the hazard to workers includes those forms of chromium considered to be non-carcinogenic (1. 2. and 3. above) as well as those considered to be carcinogenic, the level for Hexavalent Chromium Compounds, shall apply.

REFERENCES

1. AXELSSON, G. and RYLANDER, R. 1980. Environmental chromium dust and lung cancer mortality. Environ. Res., 23, 469-76.

2. AXELSSON, G., RYLANDER, R. and SCHMIDT, A. 1980. Mortality and incidence of tumours among ferrochromium workers. Br. J. Ind. Med., 37, 121-7.

3. BIDSTRUP, P.L., 1971. Chromium, alloys, compounds, in 1971. International Labour Office, Geneva.

4. BIDSTRUP, P.L., 1983. Effects of chromium compounds on the respiratory system. In chromium: Metabolism and Toxicity. 31-50, ed. by D. Burrows. CRC Press, Inc. Boca Raton, Florida, U.S.A.

5. BRINTON, H.P., FRASIER, E.S. and KOVEN, A.L. 1952. Morbidity and mortality experience among chromate workers. Public Health Reports, 67, 835-47.

6. BURROWS, D. (ed.) 1983. Chromium Metabolism and Toxicity. CRC Press Inc., Boca Raton, Florida.

7. CIKRT, M. and BENCKO, V. 1979. J. Hyg. Epidemiol. Mikrobiol., Immunology. 23, 241-246.

8. COOPER, W.C. 1983. Mortality in employees of three plants which produced chromate pigments, 45 pp. The Dry Color Manufacturers' Association, Arlington, VA, U.S.A.

9. CRONIN, E. 1980. Contact Dermatitis. Churchill Livingstone, Edinburgh, London, New York.

10. DANIELSSON, B.R.G., HASSOUN E. and DENCKER, L. 1982. Embryotoxicity of chromium: Distribution in Pregnant Mice and Effects on Embryonic Cells in vitro. Arch. Toxicol. 51: 233-245.

11. DAVIES, J.M. 1978. Lung-cancer mortality of workers making chrome pigments. Lancet, (1), 384.

12. DAVIES, J.M. 1979. Lung-cancer mortality of workers in chromate pigment manufacture: An epidemiological survey. J. Oil Colour Chem. Assoc., 62, 157-63.

13. DAVIES, J.M. 1984a. Lung mortality among workers making lead chromate and zinc chromate pigments at three English factories. Br. J. Ind. Med., 41, 159-69.

14. DAVIES, J.M. 1984b. Long-term mortality study of 57 chromate pigment workers who suffered lead poisoning. Br. J. Ind. Med., 41, 170-8.

15. DONALDSON, R.M. and BARRERAS, R.F. 1966. Intestinal absorption of trace quantities of chromium. J. Lab. Clin. Med. 68, 484, 1966.

16. FRANCHINI, I., MAGNANI, F. and MUTTI, A. 1983. Mortality experience among chromeplating workers: Initial findings. Scan. J. Work Environ. Health, 9, 247-52.

17. FREGERT, S. and HORSMAN, H. 1964. Allergy to trivalent chromium. Archives of Dermatology, 90, 4-6.

18. FREGERT, S. and OVRUM, P. 1965. Chromate in Welding Fumes with Special Reference to Contact Dermatitis. Acta Dermatol Veneral 43, 119-24.

19. GAFAFER, W.M. (ed.) 1953. Health of Workers in Chromate Producing Industry: A study. U.S. Public Health Service, Division of Occupational Health, Pub. No. 192, Washington, D.C.

20. GALE, T.F. 1982. The embryo toxic response to maternal chromium trioxide exposure in different strains of hamsters. Environ. Res. 29, 196-203.

21. GOVERNMENT OF INDIA, 1953. Report No. 1, p. 24, Ministry of Labour.

22. GYLSETH, B., GUNDERSEN, N. and LANGARD, S. 1977. Evaluation of chromium exposure based on a simplified method for urinary chromium determination. Scand. J. Work Environ. Health, 90, 4-6 and 3, 28-31.

23. HAMMOND, P.B. and BELILES, R.P. 1980. Metals in Toxicology. In: The Basic Science of Poisons, 2nd ed., Doull, J., Klassen, C.D., and Amdur, M.O., eds. Macmillan, New York, 409.

24. HAYES, R.B. 1982. Carcinogenic effects of chromium. In: Biological and Environmental Aspects of Chromium, Topics in Environmental Health, Vol. 5, pp. 221-47, ed. by S. Langard. Elsevier Biomedical Press, Amsterdam.

25. KORALLUS, V., LANGE, H., NESS, A., WUESTEFELD, E., and ZWINGERS, T. 1982. Relationships between precautionary measures and bronchial carcinoma mortality in the chromate-producing industry. Arbeitsmedizin, Socialmedizin, Preventivmedizin 17(7), 159-167.

26. KUMPULAINEN, J.T., WOLF, W.R., VEILLON, C. and MERTZ, W. 1979. Determination of chromium in selected United States diets. J. Agric. Food Chem., 27, 490-4.

27. LANGARD, S. 1983. The Carcinogenicity of Chromium Compounds in Man and Animals in Chromium Metabolism and Toxicity. Burrows, D. ed. Boca Raton, Florida, U.S.A.

28. LANGARD, S., ANDERSON, Aa. and GLYSETH, B. 1980. Incidence of Cancer among Ferrochromium and Ferrosilicon Workers. Br. J. Ind. Med., 37, 114-20.

29. LANGARD, S. and HENSTEN-PETTERSEN, A. 1981. Chromium Toxicology. In Systematic Aspects of Biocompatibility, pp. 143-61, ed. by D.F. Williams, CRC Press, Boca Raton, Florida, U.S.A.

30. LANGARD, S. and NORDHAGEN, A. - L. 1980. Small animal inhalation chambers and the significance of dust ingestion from the contaminated coat when exposing rats to zinc chromate. Acta Pharmacol. Toxicol., 46, 43-6.

31. LANGARD, S. and NORSETH, T. 1975. A cohort study of bronchial carcinomas in workers producing chromate pigments. Br. J. Ind. Med., 32, 62-5.

32. LANGARD, S. and NORSETH, T. 1979. Cancer in the gastrointestinal tract in chromate pigment workers. Arh. Hig. Rada Toksikol., 30, Suppl., 301-4.

33. LANGARD, S. and VIGANDER, T. 1983. Occurrence of lung cancer in workers producing chromium pigments. Br. J. Ind. Med., 40, 71-4.

34. LEVIS, A. G., and MAJONE, F. 1979. Cytotoxic and clastogenic effects of soluble chromium compounds on mammalian cell cultures. Br. J. Cancer, 40, 523-533.

35. LEVIS, A. G. and MAJONE, F. 1981. Cytotoxic and clastogenic effects of soluble and insoluble compounds containing hexavalent and trivalent chromium. Br. J. Cancer, 44, 219-236.

36. LIM, T.H., SARGENT III, T., and KUSUBOV, N. 1983. Kinetics of trace element Chromium (III) in the human body. Am. J. Physiol., 244: R445-R454.

37. MACHLE, W. and GREGARIUS, F. 1948. Cancer of the Respiratory System in the United States Chromate Producing Industry. Public Health Reports, 63, 1114-27.

38. MAJONE, F., and LEVIS, A.G. 1979. Chromosome aberrations and sister chromatid exchanges in Chinese hamster cells treated in vitro with hexavalent chromium compounds. Mutation Res., 67, 231-238.

39. MALI, J.W.H., VAN KOOTEN, W.J. and VAN NEER, F.E.J. 1963. Some aspects of the behaviour of chromium compounds in the skin. J. Invest. Derm. 41, 111-22.

40. MANCUSO, T.F. 1951. Occupational cancer and other health hazards in a chromate plant: A medical appraisal. II. Clinical and toxicologic aspects. Ind. Med. Surg., 20, 393-407.

41. MANCUSO, T.F. and HUEPER, W.C. 1951. Occupational cancer and other health hazards in a chromate plant: A medical appraisal. I. Lung cancers in chromate workers. Ind. Med. Surg., 20, 358-363.

42. MERTZ, W. 1969. Chromium occurrence and function in biological systems. Physiol. Rev. 49(2), 163-239.

43. NAS (National Academy of Sciences) 1974. Medical and Biological Effects of Environmental Pollutants: Chromium. Washington, D.C., National Academy Press.

44. NIEBOER, E., YASSI, A., HAINES, A.T. and JUSYS, A.A. 1984. Effects of Chromium on Human Health. Ontario Ministry of Labour.

45. NIOSH. (National Institute for Occupational Safety and Health) 1979. Registry of the Toxic Effects of Chemical Substances (RTECS).

46. PEDERSON, N. and BANG. 1982. The effects of chromium on the skin in Biological and Environmental aspects of chromium. Langard (ed.) Elsevier Biomedical Press.

47. POLAK, L., TURKJH, J.L. and FREY, J.R. 1973. Studies on contact hypersensitivity to chromium compounds. Prog. Allergy, 17, 145-226.

48. PRINCI, F., MILLER, L.H., DAVIS, A.,and CHOLAK, J. 1962. J. Occup. Med. 4, 301.

49. Public Health Service Publication 192: 1953. Federal Security Agency, Public Health Service, Division of Occupational Health of the Bureau of States Services.

50. SAYATO, Y., NAKAMURO, K., MATSUI, S. and ANDO, M. 1980. Metabolic fate of chromium compounds. I. Comparative behaviour of chromium in rat administered with $Na_2{}^{51}CrO_4$ and CrO_3. J. Pharm. Dyn. 3, 17-23.

51. STELLA, M., MONTALDI, A. 1982. Clastogenic effects of chromium on human lymphocytes in vitro and in vivo. Mut. Res. 101, 151-164.

52. STERN, R. M. 1982. Chromium compounds: production and occupational exposure. In Biological and Environmental Aspects of Chromium, Topics in Environmental Health, Vol. 5, pp. 5-47, ed. by S. Langard. Elsevier Biomedical Press, Amsterdam.

53. TOLA, S., KILPIO, J., VIRTAMO, M. and HAAPA, K. 1977. Urinary chromium as an indicator of the exposure of welders to chromium. Scand. J. Work Environ. Health, 3, 192-202.

54. UNDERWOOD, E. J. 1977. Trace Elements in Human and Animal Nutrition, 4th ed., pp. 258-70. Academic Press, New York.

55. U.S. EPA. 1984. - Health Assessment Document for Chromium. Final Report, Research Triangle Park, North Carolina.

56. WATERHOUSE, J.A.H. 1980. Cited in Effects of Chromium Compounds on Human Health, 1984, McMaster University, Hamilton, Ontario.

57. WEAST, R.C. ed. 1973. Handbook of Chemistry and Physics, 61st edition. CRC Press, Cleveland.

58. WHITE, L.R., JAKOBSEN, K. and OSTGAARD, K. 1979. Comparative toxicity studies of chromium-rich welding fumes and chromium on an established human cell line. Environ. Res. 20, 366-374.